RAPID COMMUNICATION

Serial long-term evaluation of neointimal stent coverage and thrombus after sirolimus-eluting stent implantation by use of coronary angiography

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Objective: Progression of neointimal stent coverage (NSC) and changes in thrombus were evaluated serially by coronary angiography for up to 2 years after sirolimus-eluting stent (SES) implantation.

Methods: Serial angioscopic observations were performed in 20 segments of 20 patients at baseline, at 6 months and at 2 years after SES implantation. NSC was classified as follows: 0, uncovered struts; 1, visible struts through thin neointima; or 2, no visible struts. In each patient, maximum and minimum NSC was evaluated. Existence of thrombus was also examined.

Results: The maximum NSC increased from 6 months to 2 years (mean (SD) 1.2 (0.4) vs 1.8 (0.4), respectively, $p=0.005$), while the minimum NSC did not change (0.7 (0.5) vs 0.8 (0.4), respectively, $p=0.25$). The prevalence of patients with uncovered struts did not decrease from 6 months to 2 years (35% vs 20%, respectively, $p=0.29$). Although there were no thrombus-related adverse events, new thrombus formation was found in 5% of 6-month, and in 20% of 2-year follow-up evaluations. The prevalence of thrombus inside the SES at baseline, 6 months and 2 years was similar (40%, 40% and 30%, respectively; $p=NS$).

Conclusions: Neointimal growth inside the SES progressed heterogeneously. Uncovered struts persisted in 20% of the patients for up to 2 years and subclinical thrombus formation was not uncommon.

Recently, occurrence of late stent thrombosis (LST) after drug-eluting stent implantation has become a major clinical concern.^{1–3} A long-term follow-up study demonstrated that LST occurs at a constant rate of 0.6% a year for up to 3 years after drug-eluting stent implantation.³ Pathological investigation showed that delayed arterial healing, characterised by an incomplete endothelialisation and persistence of fibrin, has a key role in the occurrence of LST.^{4,5} Moreover, a powerful predictor of LST is the existence of uncovered struts without endothelialisation.⁵ We therefore suggested that the uncovered struts of a sirolimus-eluting stent (SES) remain for an extended period of time.

Coronary angiography provides direct visualisation of the lumen and detailed information on the condition of neointimal stent coverage (NSC) and thrombus.^{6–8} This imaging modality has the advantage of allowing the identification of an intracoronary thrombus.⁸ Presently, no long-term angioscopic follow-up data after SES implantation are available. Here we present our findings from angioscopic examination, focusing on the long-term serial changes in the NSC, especially the uncovered stent struts, and the presence of thrombus inside the SES.

PATIENTS AND METHODS

Patient group

Serial angiographic and angioscopic follow-up examinations after SES (Cypher; Cordis Corp, Miami Lakes, Florida, USA) implantation were performed for 20 segments in 20 patients. Exclusion criteria were (a) acute myocardial infarction within 48 hours from onset; (b) contraindication to aggressive antiplatelet treatment; (c) restenotic lesions; (d) lesions of coronary bypass grafts; (e) low ejection fraction of the left ventricle ($<30\%$); (f) unprotected left main disease or ostial lesions; and

(g) tortuous vessels or heavily calcified vessels proximal to the target lesions. All patients received dual antiplatelet treatment (aspirin + ticlopidine) for more than 48 hours before the stenting for the prevention of acute or subacute thrombosis. During this study period, clopidogrel had not been approved for clinical use in Japan. The medical ethics committee at our hospital approved this study, and written informed consent was obtained from all patients before catheterisation.

Clinical demographics

Patient demographics were obtained by hospital chart review. Culprit lesions (target lesions of the stenting) were identified by a combination of electrocardiographic findings, wall motion abnormalities on left ventriculography or echocardiographic findings, and angiographic lesion morphology. A serum creatinine value $\geq 180 \mu\text{mol/l}$ or regular haemodialysis was used to define chronic renal failure. The ejection fraction of the left ventricle was measured by a ventriculography or echocardiography.

Coronary angioscopic imaging

The coronary angioscopic procedure has been previously reported.⁷ Serial angioscopic examinations were scheduled immediately, 6 months, and 2 years after the SES. Culprit lesions and the entire stented segments were observed with an angioscopic catheter. Angioscopic images were recorded on digital videotape for later analysis and the exact position of the angioscopic catheter at the observed segment was recorded by fluoroscopy to ensure a reliable comparison.

Abbreviations: LST, late stent thrombosis; NSC, neointimal stent coverage; SES, sirolimus-eluting stent

Definition and analysis of angioscopic findings

A thrombus was defined as a coalescent red or white superficial or protruding mass, but clearly a separate structure that remained despite being flushed with a saline solution.⁷ The extent of the NSC was evaluated by a grading system, according to our previous report.⁶ In brief, NSC was classified as follows: 0, uncovered struts; 1, visible struts through thin neointima; or 2, no visible struts under the neointima (complete coverage). Stent struts located at the orifice of the side branches were excluded from this evaluation. In each patient, the grade of the best-covered segment was defined as the maximum NSC and that of the worst-covered segment was defined as the minimum NSC. Based on the position of the angioscopic catheter on fluoroscopy, the same segments were evaluated at the 6-month and 2-year follow-up. Two observers who were unaware of the patients' information analysed the angioscopic images, and intra- and interobserver agreements were evaluated.

Clinical follow-up

Regular clinical follow-up visits occurred every month or every other month for up to 2 years after stenting. Major adverse cardiac events were defined as an acute coronary syndrome, cardiac sudden death and repeat target lesion revascularisation.

Statistical analysis

Data are presented as mean (SD). Categorical variables are presented as frequencies and were analysed by either χ^2 test or Fisher exact test. Discontinuous data (grade of the NSC) were tested by the Mann–Whitney U test with the Bonferroni's correction after the Kruskal–Wallis test. A p value of <0.05 was considered to be significant.

RESULTS

Clinical demographics

Table 1 summarises the clinical demographics of the patients. Dual antiplatelet treatment was discontinued in two patients 6 months after the SES implantation based on the angioscopic confirmation of complete NSC. These two patients thereafter received aspirin monotherapy while the other 18 patients continued to receive dual antiplatelet treatment. The reference diameter of target lesions was 2.82 (0.24) mm. Stent deployment pressure was 17.8 (3.6) atm, and dilatation after stenting was added in all procedures.

Table 1 Clinical demographics

Patients	
Age (years), mean (SD)	65 (8)
Gender, male	19 (95)
Coronary risk factors	
Diabetes mellitus	8 (40)
Dyslipidaemia	14 (70)
Hypertension	9 (45)
Current smoking	8 (40)
Obesity	6 (30)
Reason for SES implantation	
Acute coronary syndrome	5 (25)
Stable coronary artery disease	15 (75)
Ejection fraction (%)	55 (11)
Chronic renal failure	2 (10)
Location of SES	
Right coronary artery	2 (10)
Left anterior descending artery	14 (70)
Left circumflex artery	4 (20)
Number of SES, mean (SD)	1.5 (0.7)
Multiple overlapping stents	5 (25)
Bifurcating stent	0 (0)

Values are numbers (%) unless stated otherwise.
SES, sirolimus-eluting stent.

Major adverse cardiac events

There were no abnormal qualitative angiographic findings, such as filling defect, haziness, or wall irregularity, within the SES segment at follow-up. One patient received target lesion revascularisation (repeat SES implantation) at the 2-year follow-up owing to angiographic late restenosis. No other major adverse cardiac events occurred during the 2-year follow-up.

Neointimal stent coverage on angiography

The values of maximum NSC at baseline, 6-month, and 2-year evaluations were 0 (0), 1.2 (0.4), and 1.8 (0.4), respectively. The maximum NSC increased significantly from baseline to the 6-month evaluation, and from the 6-month to 2-year evaluation ($p<0.001$ and $p=0.005$, respectively). The values of minimum NSC at baseline, 6-month, and 2-year evaluations were 0 (0), 0.7 (0.5), and 0.8 (0.4), respectively. At the 6-month and 2-year follow-ups, the minimum NSC was higher than at baseline (baseline vs 6-month; $p<0.001$, and baseline vs 2-year; $p<0.001$). The minimum NSC did not increase significantly from the 6-month to 2-year follow-up ($p=0.25$) (fig 1). Uncovered struts, grade 0 of the NSC, were found in 20 patients (100%) at baseline, seven patients (35%) at the 6-month follow-up, and four patients (20%) at the 2-year follow-up. The prevalence of patients with uncovered struts did not decrease from the 6-month to 2-year follow-up ($p=0.29$). Intra- and interobserver agreements of grade of the NSC were 95% and 90%, respectively.

Thrombus on angiography

At baseline, intracoronary thrombi were observed in eight patients (40%). During the follow-up period, residual thrombi were found in seven patients (35%) at 6 months and in two patients (10%) at 2 years. One thrombus in one patient (5%) was newly recognised at 6 months and persisted for up to 2 years. Additionally, three thrombi in three patients (15%) were newly found at the 2-year follow-up. New thrombus formation was recognised in 1/7 (14%) patients with uncovered struts at 6 months and in 3/4 (75%) patients with those at 2 years. Three of four (75%) of the new thrombi were attached to the uncovered struts. All four patients who had newly formed thrombi received dual antiplatelet treatment up to 2 years. As a result, the prevalence of thrombi at baseline, 6-month follow-up and 2-year follow-up was 40%, 40% and 30%,

Figure 1 Serial changes in the maximum and minimum neointimal stent coverage (NSC). Maximum NSC on angiography increased from the 6-month to 2-year follow-up, while minimum NSC did not change between the 6-month to 2-year follow-up. For comparison of the maximum NSC, * $p<0.05$ vs baseline, and † $p<0.05$ vs the 6-month follow-up; for comparison of the minimum NSC, † $p<0.05$ vs baseline.

respectively (fig 2), and they did not differ one from another ($p=0.51$). Intra- and interobserver agreements of the prevalence of thrombi were 100% and 95%, respectively.

DISCUSSION

This investigation demonstrated that incomplete NSC persisted in 20% of the patients for up to 2 years, and 30% of the patients had subclinical thrombi within the SES segments at the 2-year follow-up.

In our series, the maximum NSC increased gradually from baseline to the 2-year follow-up. From this perspective, the angiographic NSC after the SES implantation advanced steadily for up to 2 years. In contrast, the minimum NSC almost reached its peak at the 6-month follow-up and did not significantly increase between 6 months and 2 years. These findings imply that the NSC within the SES segment progressed irregularly and support recent pathological findings.⁵ Moreover, the prevalence of patients with uncovered struts did not decrease from 6 months to 2 years. Our results suggest that struts which achieve coverage by the neointima with difficulty may remain as uncovered struts for an extended period of time. The uncovered struts, the most important measure of the angiographic findings, persisted in 20% of the patients for up to 2 years. Nevertheless, no thrombus-related adverse events occurred in this study group. Possibly, the existence of the uncovered stent struts is not an absolute condition, but a necessary condition for the occurrence of LST. In other words, when uncovered struts are present, additional factors, such as discontinuation of the antiplatelet treatment,¹ antiplatelet resistance,⁹ intrinsic thrombogenicity, or coronary flow problems, may trigger the development of LST.

The prevalence of thrombus including original, residual and newly developed thrombus did not decrease from baseline to 2 years. Previous postmortem research showed that dual antiplatelet treatment was continued in 18/23 (78%) patients who died of LST after drug-eluting stent implantation.⁵ Our angiographic observation also demonstrated that in-stent thrombus within the SES segments could arise during dual antiplatelet treatment. In this study, 75% of newly formed thrombi attached to the uncovered struts. These angiographic findings suggested that in-stent thrombus formation in the late phase was caused by the existence of uncovered struts without neointima. In one case, the uncovered struts could not be identified around the thrombus. Possibly, detection of the

uncovered struts by angiography was limited, because the thrombus might have concealed the underlying uncovered struts. Although none of the thrombi identified by angiography contributed to the occurrence of LST, our angiographic investigation supported the premise that the uncovered struts of the SES persisted for a long time and that in-stent thrombus formation originated in the uncovered struts without neointima. Our results suggest that patients with uncovered struts have a potential risk for the occurrence of LST.

The US Food and Drug Administration recommends the continuation of dual antiplatelet treatment for longer than 12 months after drug-eluting stent implantation. Nevertheless, there is no scientific evidence of the effect of discontinuation of dual antiplatelet treatment at 12 months after drug-eluting stent implantation. In this study, analysis of the clinical factors affecting persistent uncovered struts or thrombus formation could not be achieved because of the small number of patients. Further large-scale studies are necessary to determine what factors influence the persistence of uncovered struts or thrombus formation. The cause of LST is probably multifactorial. Furthermore, patient-related factors (which vary from patient to patient) may contribute to persistent uncovered struts or thrombus formation. Results of this study do not confirm the optimal duration of antiplatelet treatment after SES implantation. Although this follow-up study had no direct linkage with LST, our angiographic findings suggest that prolonged dual antiplatelet treatment is required for the prevention of LST for some patients who underwent drug-eluting stent implantation, especially those with uncovered stent struts or in-stent thrombus.

There were several limitations to this study. Although our findings were based on observations in a relatively small number of patients, serial angiographic observation showed detailed features inside the SES. In general, the angiographic evaluation was not quantitative. Nevertheless, the most important findings in this study were the qualitative identification of the uncovered struts and thrombi.

In conclusion, the serial angiographic follow-up observations after the SES implantation demonstrated that an incomplete NSC, recognised as uncovered stent struts, persisted for a long time, and that thrombus formation within the SES segment originated in the uncovered struts. Subclinical thrombus identified by angiography was not a rare phenomenon. Further careful attention to the occurrence of LST in patients with uncovered stent struts and in-stent thrombi is required.

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Conflict of interest: None.

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Figure 2 Frequency of in-stent thrombus. At baseline, 8/20 (40%) patients had a thrombus. A residual thrombus was observed in seven (35%) patients at the 6-month follow-up and in two (10%) patients at 2-year follow-up. A new thrombus arose in one (5%) patient between baseline and 6 months, and in three (15%) patients between 6 months and 2 years. The frequency of in-stent thrombus was similar during the follow-up period.

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IMAGES IN CARDIOLOGY

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Incidental patent foramen ovale detected by 64-detector row CT before radiofrequency ablation therapy

This patient attended for pre-radio frequency ablation planning for drug refractory atrial fibrillation. The only abnormality demonstrated by transoesophageal echocardiography was a moderately dilated right atrium (RA). In our institution, 64-detector row computed tomography (CT) is now used as part of the pre-radio frequency ablation procedure. CT confirmed the transoesophageal echocardiography findings—normal pulmonary venous anatomy and a previously undiagnosed small patent foramen ovale (PFO).

Panel A in axial section demonstrates a subtle flush of contrast in the RA at the interatrial septum; coronal and oblique reformations confirm a small jet of contrast from the left atrium (LA) to the RA (panels B and C, respectively) through a small PFO flap valve (black arrowhead); panel D helps to illustrate the PFO (white arrowhead) using the “Cardiac Transparency” tool (GE Healthcare Technologies, Waukesha, USA). This is of clinical significance in this patient since a septal puncture during the procedure can be avoided.

During breath-hold CT with a contrast bolus tracking technique, saline bolus chaser and appropriate scan timing, a marked differentiation in contrast enhancement between the right and left chambers may be produced, enabling even small left to right shunts to be appreciated. With high spatial and temporal resolution, fine interatrial septal detail may also be delineated. It must be

remembered that “swirls” of contrast may be seen in the RA of a structurally normal heart during CT coronary angiography owing to the mixing effect of non-contrast-enhanced blood from the inferior vena cava, the saline bolus and

residual contrast in the right heart; thus careful use of isotropic multiplanar reformation is required.

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